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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,105	01/16/2001	Donald S. Karanewsky	480140.442C1	8244

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SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 6300
SEATTLE, WA 98104-7092

EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1653	9

DATE MAILED: 12/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/765,105	Applicant(s) Karanewsky
	Examiner David Lukton	Art Unit 1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 24, 2002*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above, claim(s) *15-23* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-14* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicants' election of Group I with traverse is acknowledged, as is the elected specie (the compound of example 223).

Claims 1-14 are examined in this Office action; claims 15-23 are withdrawn from consideration.

*

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,197,750. Although the conflicting claims are not identical, they are not patentably distinct from each other; there is overlap of the claimed genera for the case of $R^{1'}$ (instant application) representing hydrogen.

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 30 of copending application Serial No. 09/745204. Although the conflicting claims are not identical, they are not patentably distinct from each other; there is overlap of the claimed genera for the case of $R^{1'}$ (instant application) representing hydrogen. [This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented].

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this

application . See 37 CFR 1.78(d)

*

This application contains sequence disclosures that are encompassed by the definitions for amino acid sequences set forth in 37 CFR 1.821. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 with regard to the sequence disclosures.

See, for example, the sequence Y-V-A-D on page 41 (line 26).

Applicant is given the time period set in this letter within which to comply with the sequence rules, 37 CFR 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six month statutory period.

*

The specification is objected to. On page 43, line 11, a table 1 is referred to, but there is no table 1 present in the application. It is suggested that reference to table 1 be deleted. If tables 1 and 2 are not present, then perhaps table 3 (pages 53-54) should be numbered as table 1.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

On pages 41-43, *in vitro* assay methods are described for inhibiting proteases. However, no data is presented. Accordingly, it is just as likely that the claimed compounds are inactive as it is that they can inhibit interleukin-1 *beta* converting enzyme. The reality in enzymology is that one cannot determine inhibitory propensity of a compound merely by viewing its structure. Proteases are very specific with regard to the substrates that they will recognize; one can take a compound which is a very effective inhibitor of a protease, and as a consequence of a very minor structural alteration thereof, inhibitory capability can be completely eliminated. The following references pertain to protease inhibitors:

- Zhang, Zhizhen (*Journal of Natural Products* **65**(7), 979-985, 2002) discloses that compounds numbered 1 and 11 were effective to inhibit aspartyl proteases of *C. Albicans*, but that all other compounds were ineffective in this regard. Many of the inactive compounds (e.g., 1a, 2, 3, 3a, 7b, 7c) were minor structural variants of compound 1. Thus, a very minor change, such as replacing a hydroxyl group with a hydrogen atom, can eliminate activity.

- Reich, Siegfried H. (*Journal of Medicinal Chemistry* **43**(9), 1670-1683, 2000) discloses (e.g., table 1) that minor structural changes can eliminate protease activity. For example, in comparing compound 1 with compound 7, one can see that repalcing a carboxyl group with a carboxamide group eliminated protease inhibitory activity.

- Iijima, Kiyoko (*Journal of Medicinal Chemistry* **42**(2), 312-323, 1999) discloses that minor structural changes can eliminate protease inhibitory activity. For example, in comparing compound 6 with compound 7 (table 1), it is evident that introduction of a single methylene group into a side chain eliminated protease inhibitory activity.

As is evident in each of Zhang, Reich and Iijima, very minor structural changes can eliminate activity. None of these three references pertain to IL-1β convertase specifically, but illustrate the realities of structure/activity relationships in protease inhibition. As it happens, the outcome of modifying structures of inhibitors is "unpredictable". Accordingly, "undue experimentation" would be required to practice the claimed invention.

In the event that *in vitro* data is provided, claim 14 will remain rejected. This claim claim is drawn to a "pharmaceutical" composition. Based upon what is stated in the specification, it is evident that applicants are asserting that if ICE can be inhibited *in vitro*, one can readily extrapolate to treatment of any autoimmune disease, inflammatory disease, or neurodegenerative disease, or that one can succeed in stimulating hematopoiesis. However, there is no evidence that this is the case. There may be a few examples in the literature of inhibiting one specific kind of inflammatory response to a given stimulus using in interleukin 1 *beta* convertase inhibitor, but it is not necessarily the case that all interleukin 1 *beta* protease inhibitors will be effective in this regard, and it is certainly not the case that any one agent is effective to achieve all that has been asserted.

It is sugggested that (a) applicants provide *in vitro* data which demonstrates that the compounds can inhibit proteases in accordance with the assertions in the specification, and that the term "pharmaceutical" be deleted from claim 14.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER